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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 10/735,203		Applicant(s) COSENZA, LAWRENCE W.	
Examiner Anne Marie S. Wehbe		Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
4a) Of the above claim(s) 3, 10, 12, 14-40 and 42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4-9, 11, 13 and 41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 June 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received. -
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

Applicant's amendment and response received on 9/21/06 have been entered. Applicant's election without traverse of the invention of Group VII, and further the election of Hpr as the species of lytic factor and trypanosoma as the species of sacromastigophoric organism is acknowledged. Applicant's election of host genes as the gene species is also acknowledged. However, as the applicant did not elect group I, drawn to the delivery system where the therapeutic agent is a gene, this election of species does not read on the elected invention, Group VII, where the therapeutic agent is a drug or prodrug.

Claims 1-42 are pending in the instant application. Of these, claims 3, 10, 12, 14-40, and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/21/06. Claims 1-2, 4-9, 11, 13, and 41 are currently under examination. An action on the merits follows.

Drawings

A new corrected drawing in compliance with 37 CFR 1.121(d) is required in this application because Figure 9 is partially illegible. It is noted that the applicant filed replacement drawings on 6/29/04 which included a petition to accept a color drawing for Figure 11. However, replacement Figure 9 is so dark that the text is not clearly legible. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and

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Trademark Office no longer prepares new drawings. The corrected drawing is required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Nucleotide and Amino Acid Sequences

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, Figures 4-8, 10 and 11 contain multiple nucleic acid and amino acid sequences which are not identified by SEQ ID NOS. It is further noted that the brief description of these drawings on pages 6-7 of the specification also fails to identify these sequences by SEQ ID NOS. In addition, page 29, lines 18 and 24 recite nucleic acid sequences and amino acid sequences respectively which are also encompassed by 37 CFR 1.821-1.825 and are not identified by SEQ ID NOS. If all of the sequences identified above have been included in applicant's paper sequence listing and CRF filed on 2/11/04, then this application can be placed in compliance by amending pages 6-7 and 29 of the specification to include the appropriate SEQ ID NOS, or by amending page 29 and submitting new drawings which include the appropriate SEQ ID NOS for Figures 4-8, 10 and 11. If these sequences are not present in the CRF and sequence listing of

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record, then a new paper sequence listing and CRF are required along with the statement that the paper copy and CRF are identical.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the rejections set forth in this office action. Failure to comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Specification

The disclosure is objected to because of the following informalities: page 3 of the specification identifies haptoglobin-related protein as “(Hrp)”. However, the remainder of the specification refers to “Hpr”, not “Hrp”.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-9, 11, 13, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

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in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim is drawn to a therapeutic delivery system comprising a therapeutic agent and a sacromastigophoric organism containing said therapeutic agent and a recombinant lytic factor, and further comprising a gene encoding a small interfering RNA related to said therapeutic agent. As noted above, the applicant has elected without traverse the invention drawn to an organism containing a drug or prodrug and the recombinant lytic factor Hpr (Haptoglobin related protein).

The specification lacks sufficient written description for 1) recombinant Hpr or nucleic acids encoding Hpr other than human Hpr (claims 1-2, 4-9, 11, 13, and 41); and 2) small interfering RNA related to a drug or prodrug. (claim 9). The specification does not provide sufficient written description for the genus of Hpr proteins or nucleic acids encoding Hpr proteins other than human Hpr protein and a cDNA encoding human Hpr. The specification discloses that factor found in human serum known as haptoglobin-related protein can induce lysis of *Trypanosoma brucei*. The specification further provides guidance for cloning the nucleic acid encoding human Hpr from the human hepatic carcinoma cell line HepG2. However, aside from the human Hpr nucleic acid sequence and encoded amino acid sequence, the specification does not provide any additional description for any other Hpr genes or proteins from any other species of animal. Further, Smith et al. teaches that serum lytic activity is only observed in some apes and Old World monkeys and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene does not express functional protein due to premature termination of translation (Smith et al. (1995) Science, Vol. 268, 284-286, see pages 285-286,

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bridging paragraph). Thus, neither the specification or the prior art provides an adequate description for any Hpr gene or protein other than human Hpr.

Further, the specification does not provide sufficient written description for any small interfering RNA related to a drug or prodrug as recited in claim 9. The specification on page 11 states that drugs are small organic molecules having a molecular weight of less than 1000 and include channel blockers, receptor blockers, steroids, opioids, platinum compounds, perenoids and alkaloids. Other than this general description, no specific examples of drugs or prodrugs are provided. Regarding small interfering RNA(siRNA), page 9 provides a general definition of small interfering RNA that these are small RNA fragments capable of degrading mRNA. However, the specification provides no further guidance as to any specific genus or species of siRNA, much less siRNA related to a drug or prodrug. The specification further fails to provide any specific guidance as to the structural, chemical, or physical properties of siRNA "related" to a drug, such that methods for identifying or isolating any such siRNA could be determined. In the absence of any such information, the skilled artisan cannot envision the detailed chemical structure of any siRNA species related to a drug or prodrug as claimed.

The Revised Interim Guidelines state, " when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genusIn an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the

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invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of siRNA related to a drug or prodrug, or of any Hpr nucleic acid or protein other than human Hpr. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of Hpr or the genus of siRNA encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai*

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Thus, for the reasons outlined above, the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

Claims 1-2, 4-9, 11, 13, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide an enabling disclosure for making any Trypanosome which contains a recombinant Hpr protein or a nucleic acid encoding a Hpr, or which additionally contains a drug or prodrug. The claims as written are broad and recite a Trypanosome containing a drug or prodrug and a recombinant lytic factor, Hpr. While claims 7-8, 11, 13, and 41 further recite that the recombinant lytic factor is upregulated by a promoter responsive to an induction species exogenous to the organism and the host, none of the claims actually recite that the Trypanosome contains a gene encoding Hpr operably linked to the promoter responsive to the induction species. The claims read on the inclusion of recombinant Hpr protein in the Trypanosome and the use of a promoter to somehow “upregulate” the contained Hpr protein. The claims as written are confusing, see the rejection under 35 U.S.C. 112, second paragraph, below. The specification discloses the construction of a vector comprising a cDNA encoding Hpr operably linked to a lysosomal targeting sequence from p67, and further operably linked to a Tet inducible T7 promoter. The specification does not teach methods for making a Trypanosome which contains recombinant Hpr protein rather than a Trypanosome which contains an inducible expression vector comprising cDNA for Hpr. Further, the prior art teaches that contacting

Trypanosomes with Hpr results in endocytosis of the protein and trafficking to lysosomes, where at least in the case of *Trypanosoma brucei brucei*, the presence of the Hpr protein in the lysosome results in lysis of the organism. However, for other species of Trypanosome, such as *Trypanosoma brucei rhodensiense*, Hpr does not have lytic activity, and Shimamura et al. hypothesize that this failure to lyse is the result of reduced endocytosis and failure to enter the lysosome (Shimamura et al. (2001) Mol. Biochem. Parasitol., Vol. 115, 227-237). As such, the prior art teaches that the presence of Hpr in *Trypanosoma brucei brucei* results in lysis of the organism such that the skilled artisan would not predict that *Trypanosoma brucei brucei* containing recombinant Hpr protein could be stably produced. Further, the prior art teaches the unpredictability of producing other species of Trypanosomes containing recombinant Hpr as it appears the Hpr is not effectively endocytosed or trafficked in these Trypanosomes. Thus, based on the state of the art for Hpr and Trypanosomes, particularly *Trypanosoma brucei* species, the lack of guidance provided by the specification, and the breadth of the claims, it would have required undue experimentation to make or use Trypanosomes containing recombinant Hpr protein.

The specification further does not provide sufficient guidance for making and using Trypanosomes containing a gene or cDNA encoding any Hpr as a drug delivery system. The specification discloses making a Trypanosome containing an expression construct comprising a gene for Hpr for use as a therapeutic delivery agent for drugs such that administration of the Trypanosome containing the drug and expression construct results in drug delivery to the host following lysis of the Trypanosome by the expressed lytic factor, Hpr. As discussed above in the rejection of the claims for lack of written description, the specification does not provide

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sufficient guidance for any nucleic acid encoding a Hpr other than a cDNA encoding human Hpr. Smith et al. teaches that serum lytic activity is only observed in some apes and Old World monkeys and that in non-human primates the only known Hpr gene is found in Chimpanzees, where the gene does not express functional protein due to premature termination of translation (Smith et al. (1995) *supra*, pages 285-286, bridging paragraph). As such, it would have required undue experimentation to isolate and use any species of Hpr gene other than human Hpr. Further, the prior art is clear that human Hpr is not active as a lytic agent against all species of Trypanosome, not even all species of *Trypanosoma brucei*. Shimamura et al., for instance, clearly teaches that *Trypanosoma brucei rhodensiense* is not lysed by Hpr or the TLF complex comprising Hpr (Shimamura et al. (2001) *supra*, page 227). The specification does not provide any specific guidance for using Hpr to lyse Trypanosomes other than *Trypanosoma brucei brucei*, and further does not provide any actual working examples demonstrating lysis of any Trypanosome through the expression of Hpr from a recombinant construct. It is also noted that the specification clearly teaches that the lysis of the Trypanosome is required to release the therapeutic agent such that inability of Hpr to lyse the majority of subspecies of *Trypanosoma brucei* would prevent the use of such Trypanosomes as drug delivery vehicles. Therefore, in view of the state of the art of Hpr and Hpr lytic activity of Trypanosomes, the limited guidance provided by the specification for lysing any Trypanosome including all subspecies of *Trypanosoma brucei*, and the breadth of the claims, it would have required undue experimentation to make and use any species of Trypanosome, including the subgenus of *Trypanosoma brucei*, as a drug delivery system.

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Regarding the subspecies of *Trypanosoma brucei brucei*, as noted above, the specification and the prior art teach that exogenously administered human Hpr or human TLF complex comprising Hpr are capable of lysing *Trypanosoma brucei brucei*. However, the claims in one embodiment are directed to intracellular expression of Hpr protein from a recombinant expression construct contained within the Trypanosome. Specifically, the specification teaches the construction of an inducible expression construct comprising the cDNA for human Hpr operatively linked to a p67 lysosomal targeting sequence and further operatively linked to an tetracycline inducible T7 promoter, as shown in Figure 9. The majority of the working examples are directed to the construction of a modified retroviral transposon to be delivered using a Trypanosome. However, note that the elected invention is drawn to the delivery of a drug or prodrug, not a virus, as the therapeutic agent. While the working examples teach the construction of an expression vector as shown in Figure 9 and described above, the examples do not include any data from any actual experiments demonstrating infection of any type of host cell followed by lysis of the host cell mediated by Hpr. Examples 5 and 6 appear to be prophetic examples describing experiments to test the ability of Trypanosomes containing an expression vector to mediate gene transfer in human or mice cells *in vitro* or *in vivo*. These prophetic examples do not demonstrate actual lysis of Trypanosome infected cells through expression of Hpr, nor do they demonstrate or suggest the delivery of any drug or prodrug using the Trypanosome.

It is further noted that the claims as written are not limited to the expression construct described in the specification and working examples. The specification teaches inducible expression of a Hpr gene modified to contain a lysosomal targeting sequence. The specification on page 34 clearly teaches that the site of action for Hpr is the lysosome. The Hpr gene itself

does not contain such a lysosomal targeting signal, since Hpr is a secreted protein. The specification teaches the addition of a 43 amino acid lysosomal-targeting sequence derived from p67 capable of targeting protein to the lysosome of a Trypanosome. In the absence of any such lysosomal targeting sequence, Hpr would be secreted by the cell such that lysis of the Trypanosome would not occur. Further, constitutive expression of lysosomal targeted Hpr would result in lysis of the Trypanosome such that a stable organism could not be made or used to deliver a drug. Thus, based on the nature of Hpr activity and the breadth of the claims, the skilled artisan would not have predicted success in making the breadth of Trypanosome organisms containing Hpr as claimed, or their use in drug delivery.

Finally, the specification fails to provide an enabling disclosure for delivering any drug or prodrug to any host cell using the modified Trypanosomes as claimed. As noted above, the working examples, both actual and prophetic, are drawn to the delivery of a provirus, not a drug or prodrug. The only guidance relevant to drug delivery provided by the specification occurs on page 18, which states that, "Non-nucleic acid therapeutic agents are packaged in a sacromastigophoric organism through electroporation or phagocytosis of liposomally packaged therapeutic agents" (specification, page 18, lines 8-10). It is noted, however, that the claims are not limited to Trypanosomes containing liposomally packaged drugs or prodrugs. The specification then points to US Patents 4,356,167, 4,873,088, and 5,843,475 are providing guidance for liposomal packaging processes. However, these patents, while teaching methods to make liposomes containing various chemical compounds or drugs, does not provide any guidance for actually introducing the liposomes into a Trypanosome or further teach the fate of such liposomes once in the Trypanosome. Neither the specification nor the prior art teach that

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drugs, either packaged in a liposome as described by any of the reference patents or not, can be stably maintained in a Trypanosome, or subsequently released to a host organism upon lysis of the Trypanosome. Further, while the specification on page 18 goes on to teach that the organism containing a non-nucleic acid therapeutic must be administered in a therapeutic amount, the specification fails to teach how much or any type of drug can be contained within a single Trypanosome or what amount of drug containing Trypanosome must be delivered to release a therapeutic amount of the drug to a host. The applicant is reminded that the Federal Circuit has stated that:

a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997). (emphasis added).

Thus, in view of the state of the art, which does not teach the inclusion of drugs or prodrugs in Trypanosomes or the use of such Trypanosomes to deliver therapeutic amounts of drugs to a host, the lack of any specific guidance for modifying a Trypanosome to contain any amount of any drug or prodrug, the lack of working examples, and the breadth of the claims, it would have required undue experimentation to make and use the Trypanosomes as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7-8, 11, 13 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a therapeutic delivery system comprising a therapeutic agent and a sacromastigophoric organism containing said therapeutic agent and a recombinant lytic factor. Claim 7, which depends on claim 1, further recites, "wherein said recombinant lytic factor is upregulated by a promoter responsive to an induction species exogenous to both said organism and said host". A "recombinant lytic factor", as recited in claim 1, is a protein, not a gene encoding a recombinant lytic factor. As such, claim 7 is confusing as it is unclear how a recombinant protein can be "upregulated" by a promoter since promoters drive expression of genes and thus can only upregulate the "expression" of a protein. Claim 11 recites that same language as claim 8. Claims 8 and 13 depend on claims 7 and 11 respectively and thus have been included in this rejection.

Claim 41 recites an organism produced by the process of claim 16, where claim 16 recites a cultured sacromastigophoric organism transfected with an expression cassette induced by a first exogenous species, the cassette comprising a first construct having a first promoter controlling expression of a lytic protein. As written, it is unclear whether the gene encoding the lytic protein is contained in the expression cassette or construct comprised in the cassette. The claim simply stated the cassette and construct comprise a promoter, not a promoter operably linked to a gene encoding a lytic protein. As such, the structure of the organism cannot be determined as it is unclear where the gene or cDNA encoding the lytic protein to be expressed is located.

Claims 1-2, 4-9, 11, 13, and 41 appear to be free of the prior art of record, as the prior art of record does not teach or suggest making a trypanosome which contains a drug or prodrug and which further contains either recombinant hpr or an expression cassette capable of expressing hpr for use as a drug delivery system in a host.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

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Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Anne M. Wehbe', with a long horizontal line extending to the right.

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: Figures 4-8, 10, and 11, and page 29 of the specification contain nucleic acid/amino acid sequences not identified by SEQ ID NOS.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE